Impact of the FDA’s Guidance Requiring a Cardiovascular Safety Screening Study to Gain Regulatory Approval of a Drug to Treat Type 2 Diabetes

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Executive Summary

The recent Food & Drug Administration (FDA) Guideline (12/08), entitled Diabetes Mellitus: Evaluating Cardiovascular Risks in New Antidiabetic Therapies to Treat type 2 Diabetes, requires a company to demonstrate empirically, prior to commercial launch in the United States (US), that a developmental drug not appear to increase the rate of cardiovascular disease. The guideline is well-intended, as type 2 diabetic patients are at approximately twice the risk for cardiovascular-related mortality than the general population.

The guideline applies even when significant improvement in glycemic control (i.e., A1c reduction) has been demonstrated, the surrogate measure sufficient previously for regulatory approval. The “screening study” involves thousands of additional patients, and an approval delay of 3 to 5 years.

The FDA’s cardiovascular screening guideline is important because the bulk of branded diabetes drugs are sold in the US. Despite a strong epidemiologic association between A1c changes and clinical cardiac event rates, little empiric data exists regarding the efficacy of current anti-diabetic drug treatments to prevent major cardiac events. This finding was highlighted in the last few years by the impact of a meta-analysis pointing to higher myocardial infarction and death rates with the highly successful glitazone, GlaxoSmithKline’s Avandia (rosiglitazone). This has led to the loss of billions of annual sales for Avandia and the termination of a rare, head-to-head clinical trial versus the other commercial glitazone, Takeda’s Actos.

Given the reliable delay from type 2 diagnosis to onset of serious cardiac events, the FDA 2008 Guideline, unfortunately, is being enacted at the beginning of the “tsunami” of exponentially increasing cardiac and other major complications from diabetes, over the next several years. Indeed, the prevalence of type 2 diabetes has doubled in the past 15 years, to nearly 26 million Americans. Therefore, a hypothetical drug with both marked A1c reduction and ability to strikingly reduce clinical cardiac events, is now subject to a long screening study process that will not yield definitive results. The consequence of this could be disastrous in terms of the numbers of type 2 diabetic patients who die due to the lack of commercial availability of such a product, which may not even be developed. Several implications for regulators, companies, physicians, patients and payers are explored in the following report, with a special emphasis on the decision to terminate the GSK Avandia vs. Actos trial in 2010, an “endangered specie” in this disease indication, seemingly at odds with the 2008 issued FDA guidelines.

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Background on Type 2 Diabetes and Treatment

Type 2 diabetes is estimated to afflict 25.8 million Americans in 2010, or approximately 8 percent (%) of the population (american diabetes association.com, 1/26/11), and nearly 1% of the diagnosed individuals die annually due directly or indirectly to diabetes (National Diabetes Statistics, 2011; http://diabetes.niddk.nih.gov/dm/pubs/statistics/#hds, accessed 2/24/11).

Another 6.2% are estimated to be undiagnosed with the disease, leading to prevalence estimates of 14% of the US population (Boyle, et al., 2010). Type 2 diabetes accounts for up to 95% of all diabetes cases (http://www.nih.gov/news/; accessed 10/31/10), and the incident rate rises with increasing age. In 2008, the percentage of diagnosed diabetes among people aged 65 to 74 years of age (19.9%) was over 14 times that of people younger than 45 years of age (1.4%; http://www.cdc.gov/diabetes/statistics/prev/national/figbyage.htm, accessed 10/31/10).

Type 2 diabetes is a recognized risk factor for coronary disease. In a meta-analysis of 102 studies, based on records of blood glucose concentration and other risk factors for coronary disease, among nearly 700,000 people, 52,765 non-fatal or fatal vascular events were analyzed (Emerging Risk Factors Collaboration, 2010). A diabetes diagnosis doubled the adjusted hazard ratio (HR) risk of coronary disease, HR = 2.0 (95% confidence interval, CI = 1.83 to 2.19) and ischemic stroke (HR = 2.27, 95% CI = 1.95 to 2.65). The results for diabetes and vascular disease were unchanged statistically by adjusting for other risk factors, such as age, sex, smoking, systolic blood pressure, or body-mass index.

The only measures proven to reduce diabetics’ probability of a clinical cardiac event, such as avoiding cigarettes, medications to improve lipid profiles and lower blood pressure levels, still leave patients with long-term diabetes at a risk of a myocardial infarction equivalent to a non-diabetic individual who has already suffered a heart attack.

In terms of specific drugs, the focus of most interest has been on GlaxoSmithKline’s (GSK’s) “blockbuster” drug to treat type 2 diabetes, Avandia (rosiglitazone). This report is not intended to disentangle all the players that, after nearly four-years, have contributed to rendering Avandia a pariah therapeutic. Instead, the focus is to explore what are the current landscape for drugs in development for type 2 diabetes in the aftermath of the Avandia.
Nissen’s Meta-Analysis of Avandia and Clinical Cardiac Events

The study with arguably the highest impact was the controversial meta-analysis of Avandia by Nissen & Wolski (2007). Avandia is a member of the class known as a peroxisome-proliferator-activator-receptor-γ (PPAR-γ), which improves glycemic control by increasing insulin sensitivity. In combination with metformin, Avandia lowered A1c levels, the primary measure of on average, about 1.5% (FDA Advisory Committee Briefing Document, prepared by GSK, 6/10/10).

Nissen & Wolski (2007) claimed higher rates of both cardiac-related mortality (64% increase) and non-fatal myocardial infarction (MI; 43% increase) among patients randomized to Avandia, versus a combination of placebo or active control groups. Using data from 42 published studies and 15,565 randomized patients, Nissen found 86 MIs and 39 deaths in the group randomized to Avandia, as compared with 72 MIs and 22 deaths in the control group. In an updated and expanded analysis including more recent studies (i.e., 56 trials that randomized 35,531 patients), Nissen & Wolski (2010) reported comparable results to their original meta-analysis.

Critical Analysis of Nissen & Wolski (2007)

The Nissen & Wolski (2007) analysis is not without its critics among diabetologists. The primary concern is that the evidence for the meta-analysis is gathered primarily from short-term studies of six months or less (range 24 to 52 weeks), with less than 1,000 individuals enrolled per study. These studies were clearly not designed to evaluate clinical cardiac event rates. Even Nissen & Wolski (2007) noted the paucity of clinical cardiac events to analyze. Of course, this is not Nissen’s fault or bias, as the drug manufacturers presumably selected patient enrollment strategies that tended to avoid clinical cardiac events that might serve to jeopardize filings for regulatory approval.

With other decisions, however, Nissen apparently did bias the meta-analysis. For example, Nissen & Wolski (2007) did not include 6 of 48 studies that met criteria for inclusion, but in which no adverse cardiovascular events were reported (Diamond, et al., 2007). Clearly, removing these “no event” studies, a priori, served to worsen the observed results for Avandia, by removing studies in which event rates were zero and equivalent between groups. Indeed, when the results from these studies are factored in, there is no statistically significant increased risk of myocardial infarction.

The efficacy of Avandia, as compared with other oral glucose-lowering medications (i.e., metformin or glyburide), as initial treatment, was evaluated among 4,360 patients with type 2 diabetes (Kahn, et al., 2006). Monotherapy failure rates, in terms of A1c changes at 5 years of follow-up were 15% with Avandia, 21% with metformin, and 34% with glyburide. Glyburide was associated with a lower risk of cardiovascular events (including congestive heart failure) than was Avandia (p<0.05), and the risk associated with metformin was similar to that with Avandia. Relevant to the Nissen & Wolski (2007) study, Kahn, et al. (2006) noted that short-term A1c changes within six months were not correlated with changes at the five years follow-up. Given the assumed relationship between A1c changes and clinical cardiac events, these results suggest that Avandia may have a more positive impact in terms of reducing coronary events, when monitored beyond the six months to one year that was the focus of the Nissen & Wolski (2007) meta-analysis. Indeed, such longer trials are recognized as the primary means to evaluate whether antidiabetic agents reduce clinical cardiac events among type 2 diabetic patients.
Avandia Competitor, Actos, and Clinical Cardiac Events

Takeda and partner Lilly had earlier sponsored the PROactive (PROspective PioglitAzone Clinical Trial In MacroVascular Events) study, the first randomized, double-blinded, placebo-controlled study to evaluate prospectively the hypothetical reduction in total mortality and macrovascular morbidity using a glucose-lowering agent (Dormandy, et al., 2005). The 5,238 patients enrolled with type 2 diabetes and macrovascular disease were randomized to receive either ACTOS or placebo in addition to other blood glucose medications and on top of standard of care treatment for cardiac patients (e.g., lipid-lowering, anti-hypertensive, anti-platelet therapeutics). This study focused on a composite of clinical cardiac events.

As reported at the European Association for the Study of Diabetes (EASD) Annual Meeting in 2005, the primary endpoint was reduced by 10%, but the groups were not significantly different statistically (p=0.095). In contrast, significantly more patients randomized to Actos developed heart failure, as compared with those randomized to placebo (11% vs 8%; p <0.0001). While not comparable to the Nissen & Wolski (2007) meta-analysis, these results do not represent a ringing endorsement of Actos. Indeed, in 1Q11, European drug regulators launched a formal probe into a potential link between Actos and an increased risk of bladder cancer (fiercepharma.com, 3/18/11).

In response to the marginalizing of Avandia, though, Actos global revenue has grown markedly. In 2006, Takeda reported ¥33.7 billion (takeda.com, 2007 Annual Report), yielding $3.37 billion US in global revenue ($1 = ¥100). By 2010, global revenue for Actos had increased to $4.5 billion US (knoll.googl.com, 2/23/11), including $3.35 billion in 2010 derived from the US (thestreet.com, 3/03/11). Given that Actos was a recipient of less than $1 billion in revenue “lost” by Avandia, it can be argued that Merck’s Januvia has also been a beneficiary of the demise of Avandia. Actos is expected to lose patent protection in 2012 (dailyfinance.com, 2/27/11).

Final Regulatory Response to Avandia

In the third quarter of 2010 (3Q10), a panel of experts was assembled by the FDA to evaluate whether Avandia should remain on the US market. The panel recommended that Avandia remain available for commercial sale (gsk.com, 7/15/10), as the evidence was suggestive of “significant safety” concerns, but not definitive that the oral agent increased the risk of clinical cardiac events (pharmalot.com, 7/14/10). In the US, Avandia was relegated to those patients for whom the drug appears to be beneficial, but is not to be prescribed to new patients (wsj.com/Mundy, 9/24/10). Moreover, GSK has agreed to halt all promotion of Avandia. In the same quarter, the European regulators legislated a stronger response to these data, withdrawing Avandia from the European market.

GSK’s Avandia was launched in 1999, and the franchise, including a combination drug, achieved peak global revenue of $3.2 billion US in 2006 (business-week.com, 2/20/10). Deutsche Bank analyst Barbara Ryan noted that Avandia prescription trends following Dr. Nissen’s (2007) report, as compared to the week prior to the release, were down 42% (cnbc.com, 6/26/07). Worldwide sales were reduced to approximately $2.2 billion in 2008 (youhavealawyer.com/Saiontz&Kirk, 4/07/09), $1.2 billion in 2009, and then slipped to $704 million in 2010 (gsk.com, 2/03/11). Regardless of the merits of the meta-analysis, which involved primarily short-term studies not designed to evaluate clinical cardiac events, there is no doubt that revenue will continue to be marginalized. One might have surmised that Avandia has lost patent protection, but this is not expected until 2012 (pharmatimes.com, 7/15/10). In contrast, lawsuits are rising, and GSK announced a 4Q10 charge-to-earnings equivalent to $3.5 billion US, due to Avandia-related, product liability (Bloomberg.com/Torsoli, 1/17/11).
FDA Guidelines (2008) Regarding Developmental Drugs to Treat Type 2 Diabetes

In the wake of the Avandia debacle, by the end of 2008, the FDA issued new guidelines that increased markedly the burden on pharmaceutical companies developing new drugs to treat type 2 diabetes (http://www.fda.gov/cder/guidance/8576fnl.pdf, 12/08). That is, although developmental drugs must demonstrate improved glycemic control, as measured by glycosylated hemoglobin (A1c) reductions, as a primary outcome measure, companies are now required to demonstrate empirically, in a screening study, that there appears to be no increased risk of cardiovascular disease, based on clinical cardiac endpoints (http://www.fda.gov/cder/guidance/8576fnl.pdf, 12/08). Dr. Nissen presented the “blue-print” for the design of the screening study at an earlier FDA advisory meeting (heartwire.com, 7/03/08).

The Phase III study will require a minimum of two years of data collection to examine the incidence of key cardiovascular event rates by the investigational agent and control group. Approvable drugs will have an upper bound of the two-sided 95% confidence interval for the estimated risk ratio of less than 1.8, in the screening study. If the result is in the 1.3 to 1.8 range, and the risk-benefit analysis otherwise supports approval, a post-marketing trial will be necessary to demonstrate that the actual upper bound of the 95% confidence interval for the estimated risk ratio is less than 1.3. The control group of choice, for the screening study was unspecified, but appears to be the biguanide, metformin (Selvin, et al., 2008).

Metformin is the first-line drug treatment, along with dietary/exercise lifestyle changes, in the most current American Diabetes Association guidelines for the treatment of type 2 diabetes (Nathan, et al., 2009).

Although a screening study, these guideline criteria will have a major impact on drug development for the treatment of diabetes. As noted, the usual six-month study to establish significant A1c reductions will no longer suffice for regulatory approval (glgroup.com, 12/22/08). Moreover, although studies conducted for regulatory filing traditionally excluded diabetic patients at increased risk for clinical cardiac events, enrolling patients with low rates of clinical cardiac events, such as an annual base-rate of 2.5%, to lower this rate to 2.0% would require a clinical study with 7,000 patients per treatment arm.

The more promising approach to meet the demands of the screening study will be to enroll patients at a much higher risk of clinical cardiac events than occur in the studies included in Nissen & Wolski (2007), such as cardiac-related mortality, non-fatal myocardial infarction, or stroke. Based on a Veterans Administration study with a composite endpoint, and an annual event rate of 5.6% (Duckworth, et al., 2008), the calculation of sample size to distinguish a 25% greater event rate over a two-year period (13.9% vs 11.1%), with a 0.05% type 1 error, and statistical power of 80%, approximately 2,200 diabetic patients would be required in each treatment arm (glgroup.com, 12/22/08). The required screening study will likely delay the US regulatory approval of a novel drug to treat type 2 diabetes by approximately four years.

This is not a theoretical exercise, as the example of Takeda’s dipeptidyl peptidase-IV (DPP-IV) oral drug, alogliptin, demonstrates strikingly. Takeda has accepted the new screening guideline, assuming that alogliptin will not be approved in the US, in the absence of clearing the safety signal, screening requirement. This interpretation follows from the finding that alogliptin has established A1c reduction in five prior Phase III double-blinded, placebo-controlled studies. That is, alogliptin was effective in reducing A1c levels, either as monotherapy (DeFronzo, et al., 2008) or when added to commonly used anti-diabetic agents (e.g., metformin, Nauck, et al., 2009; glitazones, Pratley, et al., 2009; sulfonylureas, Pratley, et al., 2008; insulin, Rogenstock, et al., 2009). Alogliptin was well-tolerated, and associated with few adverse events.
Clinical Trials of Developmental Drugs to Treat type 2 Diabetes with Clinical Cardiac Outcomes

**Takeda's DPP-IV, Alogliptin**

Takeda is recruiting currently for a 5,400-patient, Phase III study of type 2 diabetes and acute coronary syndrome (ACS, 15 to 90 days prior to randomization), with the primary outcome the clinical cardiac event rate (composite of cardiovascular death, non-fatal MI, and non-fatal stroke), for alogliptin (25-mg, once daily with normal or mild renal impairment; 12.5-mg once daily, for patients with moderate renal impairment). The control group is placebo, and enrolled patients will have inadequate glycemic control while prescribed one or more non-glucagon-like peptide-1 (GLP-1) drugs, which includes the DPP-IV drugs, to treat diabetes (clinicaltrials.gov #NCT00968708, updated 3/04/11). Inclusionary drugs consist of the range of background oral anti-diabetic agents, as noted in the prior paragraph, as well as insulin. The study was initiated in 9/09, and is expected to last up to 4.75 years.

To my knowledge, this represents an unprecedented study in the history of drug development in the treatment of type 2 diabetes. That is, a double-blinded clinical cardiac outcome study, with an appropriately dosed control group, notwithstanding alogliptin versus placebo, because of background therapeutics (e.g., sulfonylureas, metformin, thiazolidinediones, and insulin), has never been conducted, prior to drug approval, for such a therapeutic agent. Indeed, it has been noted that few studies of developmental drugs are conducted, with clinical outcomes rather than surrogate measures, even using inadequate response to the standard-of-care regimen as the control group, plus placebo (Hochman & McCormick, 2010).

Quintiles, a contractual research organization (CRO) that claims to have conducted over 100 diabetes trials since 2006, reports that the cost per patient for a type 2 diabetes trial ranges from $15,000 to $30,000 (Nicosia JD. New FDA Guidances On Anti-Diabetes Therapies Change the Landscape of Drug Development, no date specified, accessed 10/28/10). Taking the average of the range, $22,500, with 5,400 patients, the projected cost of this Phase III study is approximately $120 million.

**Takeda Motivate by the Successful Launch of Merck’s Januvia**

Clearly contributing to the Takeda decision to take this unprecedented step is that the revenue generated by the class of DPP-IV drugs, which in 2010 combined for $3.92 billion, including $3.35 billion (merck.com, 2/03/11) for the combined Januvia/Janumet (Januvia and metformin pill) franchise (72.7% from Januvia), an increase of 29% to the corresponding franchise revenue in 2009. Approximately 70% of the Januvia revenue was derived in the US, according to IMS Health (cited by cphi-online.com/Staton, 1/31/11). In contrast, Novartis’ DPP-IV, Galvus recorded $391 million in 2010, up 122% versus 2009 (novartis.com, 1/28/11). The third DPP-IV drug, Onglyza, is partnered by Bristol-Myers and Astra Zeneca. Onglyza registered global revenue of $225 million ($158 million, bristolmyers.com, 1/27/11, and $67 million, astraZeneca.com, 1/31/11) in 2010.
Merck’s Januvia (sitagliptin) was approved in the 3Q06 (nytimes.com/ Berenson, 10/18/06), and Bristol-Myers/Astra Zeneca’s Onglyza (saxagliptin) was approved in 3Q09 (endocrinetoday.com, 11/01/09). Galvus was not approved in the US, due to skin toxicity, but was approved in Europe in 4Q07 (medicalmarketing&media.com, 10/01/07). The two drugs approved in the US are priced comparably, at about $5.72 per day (fiercepharma.com, 8/03/09).

Briefly, it is unusual to find a blockbuster drug approved since 2005, and Januvia meets these criteria. That is, only one drug per year, on average, has attained $1 billion or greater annually in global revenue, although over 130 new molecular entities have been approved by the FDA, in the years 2005 to 2010 inclusively (www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM247465.pdf).

Besides Merck’s Januvia/Janumet, the other blockbuster drugs were as follows (2010 revenue in parentheses): Celgene’s Revlimid ($2.47 billion; celgene.com, 1/10/11), Roche/Novartis’ Lucentis ($2.9 billion; zacks.com, 1/28/11; roche.com, 2/02/11), Pfizer’s Prevnar-13 ($2.47 billion; Pfizer.com 2/01/11), Elan/Biogen’s Tysabri ($1.2 billion; marketwatch.com, 2/01/11), which was removed from the US market in 2/04, three months after launch, and then returned to the market, nearly 18 months later, and Pfizer’s Sutent ($1.07 billion; Pfizer.com, 2/01/11).

Based on the commercial results, one might assume that Januvia was superior clinically to Onglyza in a head-to-head clinical trial. In the one double-blinded clinical study, with A1c reduction as the primary endpoint (N = 801), however, Onglyza was found to be “non-inferior” to Januvia (-0.52 vs -0.62 absolute a1c reduction, respectively, p>0.05; astrazeneca.com, 10/05/09). The safety profile of the two DPP-IV drugs was also comparable. Indeed, the DPP-IV drugs are assumed not to differ from one another in terms of A1c reduction, with the level of A1c reduction related systematically more to the baseline level of A1c of type 2 patients than to which member of the DPP-IV class is being investigated (Kuzner, 2006). That is, greater A1c changes are observed when patients with higher A1c baseline levels are tested, and smaller mean changes observed among studies that recruit patients with lower baseline A1c levels (Bloomgarden, 2007).

The global revenue for Januvia, particularly in the US, provides an incentive for Takeda to conduct an expensive Phase III trial to gain regulatory approval for alogliptin. But the inability to differentiate from a market leader, in general, predicts the lack of commercial success of what are known as “me too” drugs since 2005. That is, a drug that shares a mechanism of action with a launched drug. A relevant example is the DPP-IV, Onglyza, which, as noted above, has marginal revenue relative to Januvia. A comprehensive argument justifying this claim, has been written at this site, on the Importance of being the Branded Pharmaceutical “First-to-Market” in 2010: Silence of the “Me-Too” Lambs, which was posted on 8/18/10).

Takeda, though, can avoid the “me too” nomenclature if alogliptin generates data that Merck’s Januvia does not have currently, that is, positive results in terms of a reduction in clinical cardiac outcomes. With 1,000 more patients than the normal screening study of 4,400 with a two-arm study, the likelihood of success (or failure) is increased accordingly. A statistically significant difference in favor alogliptin would represent a far more impressive clinical outcome, at the time of launch, than the surrogate measure of A1c reduction, which was sufficient at the time of Januvia approval in the US in 2006. If alogliptin can meet or exceed the 2008 clinical guidance for developmental drugs to treat diabetes (http://www.fda.gov/cder/guidance/8576fni.pdf, 12/08), one would then predict that much of the Januvia/Janumet share would quickly shift to alogliptin, upon launch of this innovative product.
In contrast, if alogliptin fails in comparison to placebo and background therapy of traditional agents, then this becomes just another “me too” DPP-IV competitor that is unlikely to be filed for regulatory approval.

**Sodium-Dependent Glucose Transporter 2 (SGLT2) Inhibiting Drugs in Development**

A novel class of oral antidiabetic agents is presumably also subject to the FDA Guidelines of 2008. Suppressing the activity of SGLT2 in the body inhibits the re-absorption of glucose in the kidney, leading to excess blood glucose excreted in urine, and thereby reducing blood glucose levels systemically (Rajesh, et al., 2010).

The SGLT2 that appears most advanced is Bristol-Myers/Astra Zeneca’s dapagliflozin, which is unique within the class by the publication of Phase III results, in terms of glycemic control. Among 24 studies listed in clinicaltrials.gov as Phase III studies, only three made reference to cardiac events. None of these studies, on its own, would meet the minimal standards of sample size or length of study, to address the screening clinical cardiac event study requirement. The largest, “A Study of BMS-512148 (Dapagliflozin) in Patients With Type 2 Diabetes With Inadequately Controlled Hypertension on an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker” (clinicaltrials.gov, #NCT01137474, updated 4/07/11), had only 1,104 subjects enrolled, albeit with only twelve weeks of data collection.

Despite the need for an estimated 4,400 patients in a two-arm study collected for at least two years (cf. Duckworth, et al., 2008), the FDA has accepted the filing of dapagliflozin, as new drug entity (NDA). The US filing included approximately 6,000 adult individuals with type 2 diabetes across 40 clinical studies, for an evaluation of the cardiovascular safety of dapagliflozin (businesswire.com, 4/08/11). The FDA will presumably receive a meta-analytic approach to clinical cardiac event rates with dapagliflozin.

Boehringer initiated a Phase III study to determine the cardiovascular safety of the SGLT2 oral agent, BI 10773, in 7/10 (clinicaltrials.gov, NCT01131676, updated 4/07/11). This is a 4,000-patient study of BI 10773 versus placebo, among patients with type 2 diabetes, initiated in 7/10, and expected to last four years.
A perusal of clinicaltrials.gov, though, does indicate that Merck is conducting its own clinical cardiac outcome trial with Januvia, utilizing a similar clinical design and composite as the Takeda study (http://clinicaltrials.gov/ct2/archive/NCT00790205, accessed 10/25/10). The trial will enroll diabetic patients who have an inadequate clinical response (baseline A1c in the range of 6.5% to 8%) in response to first-line and potentially other anti-diabetic agents. Januvia was dosed as follows: 100-mg once daily for patients with normal or mildly impaired renal function, or 50-mg tablet once daily for patients with moderately impaired renal function. The study began enrollment in 11/08.

The Merck trial, though, is 14,000 patients with pre-existing cardiovascular disease, as compared to the 5,400 ACS patients in the corresponding Takeda study. Each of the clinical studies contains two treatment arms, with the same duration of four-to-five years to complete. Is one to conclude that the biostatisticians at Merck and Takeda have markedly different ways of deriving an appropriate power analysis, given a comparable research design? Unlikely, as there seems to be a more parsimonious explanation for this radical difference in trial sample sizes.

For Merck, it is arguably about achieving a “balancing act”, being proactive, albeit in a defensive manner. Clearly, Takeda is conducting a “semi-threatening” study, although Takeda is not attempting a full head-to-head, clinical trial comparing alogliptin against sitagliptin (i.e., Merck’s Januvia). By 2015, when alogliptin may finally be launched, the Januvia franchise will likely be generating close to $5 billion annually. Accordingly, conducting such a clinical cardiac outcome study has inherent risks for Merck, much more at stake than for Takeda.

If Januvia results in higher rates of MI and other clinical cardiac events, as compared to the control group, this will lead to a quick and violent end to Januvia/Janumet blockbuster sales. This outcome is predictable regardless of the results from the Takeda study for alogliptin. This fate was documented in the earlier review of GSK’s Avandia (rosiglitazone).

While enrolling 14,000 into the Merck clinical study may slow enrollment, it will not prevent and, ironically, may expedite the termination of the study, relative to the Takeda study of 5,400 patients. That is, if Januvia proves to have significantly more clinical cardiac composite events than the control group (or vice versa). That is, the larger “N” is more likely to lead to a definitive study result in a shorter period of time (cf. “central limit theorem”).

For Merck, the choice of a 14,000-patient study is likely to represent the internal calculation that the most likely clinical outcome is no significant differences between treatment arms of Januvia versus placebo. It is in this more probable scenario that the over-enrolled study may prove beneficial commercially for Merck. If there is no overall efficacy for Januvia versus placebo, given standard background antidiabetic medications, then the 14,000 patients in a two-group design provides the statistical “horse-power” to conduct post-hoc analyses, with the intent of finding one or more significant effects among subgroups that could salvage this otherwise neutral study for Januvia.
Importance of the United States to Global Sales of Branded Drugs to Treat Diabetes

The US is critical to the type 2 diabetes global market for branded drugs, and represents an anomalous disease indication, in this regard, based on revenue. In general, IMS estimates that global prescription drugs will total $880 billion in 2011, with about $325 billion derived from the US, a percentage of 36.9% (worldpharmanews.com, 12/20/10).

To draw the contrast, the obvious example would be to categorize Merck’s Januvia/Janumet into US and ex-US sales, to demonstrate the alleged US dominance in the global market for antidiabetic agents. Unfortunately, Merck does not provide these data in its quarterly earning report. Instead, in 4Q10, for example, Merck simply provided global revenue for Januvia ($675 million) and Janumet ($288 million), for a total of $963 million, up 42% versus 4Q09 (merck.com, 2/03/11). Januvia revenue grew double-digits across all markets, and is now in the top 75% of all diabetes treatments in the top 20 markets (UBS/Goodman, 10/29/10). Earlier it was estimated that 70% of the Januvia revenue was derived in the US, based on IMS Health data (cited by cphi-online.com/Staton, 1/31/11).

The percentage of global sales driven by US sales can be calculated directly with other antidiabetic agents. For example, the successful injected GLP-1 drug, Amylin/Lilly’s Byetta (exenatide) registered $175 million in worldwide sales of Byetta in 4Q10 (lilly.com, 1/27/11). US sales of Byetta were $136 million, whereas corresponding international sales were $38.2 million. Thus, 77.7% of Byetta global revenue was derived in the US in 4Q10. For the full year of 2010, worldwide Byetta sales were $710 million, with US Byetta sales at $559 million, while sales outside the US increased registering $151 million. Similarly, 78.7% of global sales of Byetta occurred in the US in 2010.

Merck, Amylin and Lilly are based in the US, and perhaps this influences the geographic basis of sales. Accordingly, perhaps an European company would have the majority of its sales internationally. For instance, in 4Q10, Sanofi’s Lantus, a successful long-acting insulin from the French-German company, registered global sales of euro894 million (sanofi.com, 2/09/11), equivalent to $1.22 billion US, for the quarter. Of the euro894 total, the US market accounted for euro533 million, or 59.6%. Emerging markets, led by Latin America and China contributed euro137 million, or 15.3%.

These examples consistently point to American sales of drugs to treat diabetes are around 60% or greater in terms of global sales. This percentage is strikingly different than the less than 40% market share the US has with regard to global prescription drug sales, in general. Clearly, gaining access to the US market, which now requires the cardiac screening study, is the key to commercial success for a branded drug to treat diabetes, type 1 and/or type 2.
Implications for Drug Development to Treat Type 2 Diabetes: More Drugs in Development Terminated

The Quintiles analysis noted that the estimated cost of a diabetes study ranged from $15,000 to $30,000 per patient, and speculated that the FDA Guideline (12/08) would increase the cost per patient by 25% to 50% (Nicosia JD. New FDA Guidances On Anti-Diabetes Therapies Change the Landscape of Drug Development; accessed 10/28/10).

In an arguably related story, the biotech, Phenomix, recently laid-off 45 employees and ended operations. The company had been developing a DPP-IV drug, dutagliptin, to treat type 2 diabetes (xconomy.com/Timmerman, 10/26/10). Notwithstanding that dutagliptin performed well in a clinical study, partner Forest terminated the deal for what was deemed “business reasons” (xconomy.com, 4/20/10). Following the termination of a partnership with Forest Labs, Phenomix was unable to find another pharmaceutical partner.

The “business reason” is arguably that the diabetes drug development process has changed strikingly, since Phenomix received $75 million in an initial payment from Forest when the partnership was signed in 4Q08 (xconomy.com/Timmerman, 10/26/10). The plan then was to conduct six clinical trials at a cost of about $150 million to $200 million. But as determined earlier, a viable approach to the FDA Guideline regarding cardiovascular safety would require, by itself, an investment of an additional estimated $64 million to $132 million (Nicosia JD. New FDA Guidances On Anti-Diabetes Therapies Change the Landscape of Drug Development; accessed 10/28/10).

The “unanticipated consequence” of the FDA Guideline regarding cardiovascular safety is that drugs in development to treat type 2 diabetes are more likely to be terminated early, due to the cost of the extra, pre-approval screening study required by regulators. Ironically, the companies had even listed a clinical cardiac trial of Phenomix’s dutagliptin versus Merck’s Januvia (N = 1,050), in terms of A1c reduction, but this study was “terminated” officially (clinicaltrials.gov, NCT01089790; updated 9/27/10).

Drug Development Determined by Large Pharmaceutical Companies

Large pharmaceutical companies seem reluctant to compete on price, following the FDA’s criterion, defined by at least a 15% relative change, in this case a 15% discount price compared to the standard-of-care, branded drug. A relevant example to this discussion is that Merck’s DPP-IV Januvia franchise generated $962 million in 4Q10 (merck.com, 2/03/11), as compared to corresponding revenue of only $105 million for Bristol-Myers/AstraZeneca’s Onglyza ($73 million, Bristol-Myers.com, 1/27/11, and $32 million, astrazeneca.com, 1/27/11). A nine-fold discrepancy in revenue exists for the most recent quarter, notwithstanding the absence of empiric data suggesting differential efficacy: safety (astrazeneca.com, 10/05/09), and comparable pricing, at less than $5/day in the US. An internet blogging site (http://www.freebeforeignpharmacy.com/pharmacy-drugs-blog/why-wont-onglyza-compete-with-januvia-on-price/; accessed 10/29/10), poses the following rhetorical question, regarding competing branded drugs: “In fact, when’s the last time you saw a pharmaceutical commercial where the drugmaker advertised that its product was cheaper than the competition? If you said ‘never,’ you’re probably right.”

But smaller companies have demonstrated a willingness to compete occasionally on price, albeit for very high priced branded drugs. For example, the moderate-sized, fomer biotech, Amgen, priced its endothelial growth factor receptor (EGFR), Vectibix (panitumumab) at a 20% discount to ImClone/Merck-Serono/Bristol-Myers/Lilly’s Erbitux (cetuximab) for the treatment of advanced colorectal cancer. The respective prices for the monoclonal antibodies were $8,000 versus $10,000 per month in the US (cancerdecisions.com, 8/10/10). Both drugs were approved on the basis of progression-free survival, rather than the preferred overall survival criterion.
In a unique move, the companies that manufacture both Erbitux and Vectibix received changes to their US labels that indicated that patients with colorectal cancers who also are positive for KRAS mutations did not benefit clinically from treatment with these monoclonal antibodies (fda.gov, 7/17/09). Unique in that the labels acknowledge that the drug is not for all patients with the disease. Erbitux also generates sales from a smaller oncology indication, head-and-neck cancer.

Vectibix had $288 million in global 2010 revenue (amgen.com, 1/24/11), whereas in 2010, Bristol-Myers recorded $662 million in revenue for Erbitux (bristolmyers.com, 1/31/11), euro820 ($1.12 billion US) registered by Merck KGaA (merckkgaa.com, 2/21/11), and Lilly listed $386 million (lilly.com, 1/27/11) in corresponding revenue. Thus, Erbitux global revenue in 2010 was $2.17 billion. This suggests that the first-to-market drug has a commercial advantage, given the absence of differentiation by the second-to-market drug, even a biologic with a significant price differential.

The Genzyme treatment for Gaucher’s disease, called Cerezyme (imiglucerase), sells for about $200,000 annually. In this disorder, the lack of the gluco-cerebrosidase enzyme causes the liver, spleen, bones, and bone marrow from functioning properly. UK-based Shire noted that the competitor to Cerezyme, Vpriv, was priced at a 15% discount to Cerezyme (pharmacychoice.com, 3/01/10). Genzyme’s leading selling drug, with about 6,000 patients prescribed the drug annually, generated ~$1.2 billion in 2008, but has suffered from manufacturing constraints in 2009 and 2010 (bioworldtoday.com, 6/17/10). Genzyme, now part of Sanofi, reported global revenue in 2010 for Cerezyme of $720 million (firstwordplus.com, 2/16/11). The low-cost competitor, Shire’s Vpriv, has started strong, with $143 million reported in 2010 (shire.com, 3/17/11).

The point is that large pharma seems loath to compete in terms of price of branded drugs, and it is only the smaller companies that are beginning to defy this “unwritten rule”. The article on the Phenomix shut-down of operations is informative. Given the marked increase in costs for drug development inherent in the required screening study for cardiovascular safety, these drugs will no longer be developed by smaller companies. That is, small and mid-size companies will likely terminate the development of “me-too” drugs to treat type 2 diabetes, based on the additional cost of the FDA’s screening study, even drugs that have the potential to be approved by regulators. This will leave Phase III drug development more concentrated in the hands of large pharma, who demonstrate empirically that they would rather stop the development of a “me too” drug than to compete aggressively on price. As noted, only the smaller companies are beginning to exert some willingness to compete on price with another large pharma. This will have the unanticipated consequence of providing less choice to patients, physicians, and payers, at a time when diabetes is a growing epidemic in the US.

Implications of the Screening Study for the Treatment of the Growing Epidemic of Type 2 Diabetes

The timing of the new FDA Guideline is interesting in light of the trends in the US prevalence of type 2 diabetes. As seen in the following graph, there is a marked increase in the number of diagnosed Americans with type 2 diabetes, particularly among those aged 45 years of age and older, starting in the mid-1990’s, and continuing currently.
A Growing Need

Current type-2 diabetes incidence rate trends point to an increase from 8 per 1,000 people to 15 per 1,000 people.

This is caused by an aging population, increased representation by minority groups who are more susceptible, and the fact that those already diagnosed are living longer.

Percentage of Civilian, Non-Institutionalized Population with Diagnosed Diabetes, by Age, United States, 1980–2008


These trends led members of the US Centers for Disease Control and Prevention (CDC) to publish recently a forecast of diabetes prevalence in the US over the next forty years (Boyle, et al., 2010). Currently, about one in 10 adults in the US has diabetes, but with an aging population, increased representation by minority groups who have higher incident rates of type 2 diabetes onset, and the fact that individuals with diabetes are living longer, reflecting improvements in the treatment of cardiovascular disease, estimates for the future range from a prevalence of diabetes from one in five to one in three. New onset diabetes cases could increase from eight per 1,000 people in 2008 to 15 per 1,000 in 2050.

There are serious adverse events associated with diabetes, as the following chart provides the prevalence of complications in people with type 2 diabetes versus people with normal blood sugar levels, based on NHANES data from 1999 to 2004.
There is a striking difference in events rates, for both macrovascular (related to the heart and large blood vessels), and microvascular complications (related to small blood vessels) due to diabetes, such as kidney disease, eye damage, and foot disorders, and much higher rates of onset of the microvascular events. For many of these events, and consistent with the earlier discussion of the power calculation for the composite clinical cardiac event endpoint need for the screening study for developmental drugs to treat diabetes, it takes many years for the serious cardiac complications of diabetes to emerge. In non-cardiac, newly diagnosed type 2 diabetic patients, the United Kingdom's Prospective Diabetes Study (UKPDS Group, 1998) demonstrated that a median of ten years of glucose control was capable of yielding marked improvements in microvascular events, but not in reducing rates of macrovascular events, such as MI. The lack of reduced Mls was in large part due to the absence of such events among newly diagnosed patients. If diabetes had been present for more than 21 years, the risk of primary CV events in patients on intensive control more than doubled (professional.diabetes.com, abstract for the American Diabetes Association, to be presented 6/24-8/11).
Recall the marked increase in the prevalence of diabetes in the US during the past 15 years. Given the delay in the clinical sequelae of diabetes, we are just at the beginning of period when the serious complications from diabetes will emerge among the rising sub-population of Americans with diabetes. Based on the differential rates of these serious complications, the CDC concludes that people with diagnosed diabetes have medical expenditures that are about 2.3 times higher than medical expenditures for people without diabetes (http://www.cdc.gov/chronicdisease/resources/publications/AAG/ddt.htm; accessed 10/31/10).

It is against this backdrop of increasing rates of diabetes, with a “tsunami” of increasing complications related etiologically to diabetes, with markedly higher direct medical costs due to diabetes, the FDA has decided to become more conservative about releasing developmental drugs to treat diabetes. There is little doubt that the 2008 FDA Guideline will delay drug approvals three to five years, at a time when there is a growing acknowledgment that our current treatments do not provide adequate glycemic control for the majority of diabetic patients.

Imagine a drug that empirically lowers mean A1c levels 1.2% above that of metformin, and is capable of lowering clinical cardiac event rates by 35% among diabetic patients. The FDA (2008) guideline will not allow this drug to be approved until the screening study results suggest no increased rates of cardiovascular disease. Given the epidemiology of type 2 diabetes, with (1) 25.8 million estimated in the US in 2010, (2) nearly 1% of the diagnosed individuals die annually due directly or indirectly to diabetes, and (3) seventy percent of these deaths will be attributed to coronary disease; accordingly, a four-year delay in regulatory approval would translate into an excess of 250,000 lives lost, based on a drug with a 3% level of efficacy reduction.

Genuine Head-to Head Trials

The highest level of clinical evidence is derived from the double-blinded, randomized, head-to-head trial, in which the standard of care, dosed appropriately for the relevant disease indication, is used as an active comparative agent for the clinical indication. Optimally, there is a placebo control, as a third treatment arm, which aids in interpretation of trial results. The primary outcome measure is a clinical endpoint, rather than a surrogate measure (e.g., cardiac-related mortality and non-fatal MI, rather than either A1c or lipid reductions). Since this is a clinical outcome study, an adequate sample of enrolled patients with sufficient disease severity will be represented, to generate an appropriate rate of relevant events, and, to theoretically demonstrate the superiority of one active treatment over another.

The absence of such head-to-head clinical trials was documented recently in a review of medication studies published in six “top medical journals” (N = 328) analyzed in terms of their comparative effectiveness (Hochman & McCormick, 2010). The bulk of the randomized studies, including those that were double-blinded, were marked by study designs that were restricted to placebo-control only, and involved developmental drugs with no active launched comparator.
Less than 15% of the studies compared active drugs to one another, and most of these comparative agents would not be considered the "standard of care", in the relevant disease indication (Hochman & McCormick, 2010). Instead, companies select a second- or third-tier drug for comparative purposes, or a first-tier at a lower or higher dose than is beneficial clinically, seemingly to reduce its efficacy : safety ratio relative to the sponsor’s agent (O’Connor, 2010). The studies evaluated were published from June 2008 through September 2009, including the Journal of the American Medication Association, The New England Journal of Medicine, The Lancet, British Medical Journal, Annals of Internal Medicine, and Archives of Internal Medicine (Hochman & McCormick, 2010).

Clearly, one reason that more head-to-head clinical trials are not conducted is because the company places its drug at risk. One salient example, also sponsored by a drug manufacturer, Bristol-Myers, which tested its lipid-lowering drug, Pravachol, versus market leader, Pfizer’s Lipitor. This was in a population of acute coronary syndrome (ACS) patients, and a composite of clinical cardiac events emerged as the primary trial outcome. This was also a post-marketing trial, as Bristol-Myers apparently felt that despite being a blockbuster drug, Pravachol generated markedly less revenue than competitors Lipitor or Merck’s Zocor. In 2003, for example, US Lipitor sales were $5.54 billion, Zocor sales were $3.28 billion, and Pravachol sales were $1.67 billion (drugs.com, accessed 722/10).

The test of high-dose Lipitor (80-mg) versus moderate-dose Pravachol (40-mg; recall that this trial was sponsored by the manufacturer of Pravachol), with only 4,162 ACS patients enrolled, yielded a significant clinical outcome in the PROVE-IT trial (Cannon, Braunwald, McCabe, et al., 2004). The risk of a major cardiovascular event or death from any cause was reduced by 3.9% absolutely and 16% relatively, in favor of Lipitor, versus Pravachol.

One might speculate that Bristol-Myers was motivated to under-power the trial, on purpose, to lower the probability of a significant difference emerging between the active statin treatments. That is, no significant differences would clearly have benefited the less potent Pravachol, as Bristol-Myers attempted to argue that low-density lipoprotein cholesterol (LDL-c) lowering to clinical cardiac event reduction was not a linear relationship as argued by Pfizer and Merck, but followed an asymptotic curve after about 20% LDL-c lowering. If the latter hypothesis was valid, then the 23% LDL-c lowering with 40-mg Pravachol should have generated comparable clinical efficacy as 80-mg Lipitor with about twice that amount of lipid lowering capability (Cannon, et al., 2004). Empirically, as noted, this was not the case as Lipitor proved to be superior to Pravachol at the doses tested.

Based on PROVE-IT, testing two treatment arms, around 4,500 patients would suffice for a legitimate ACS trial. This is consistent with the calculation of the sample size required to distinguish an approximate 25% greater event rate over a two-year period (13.9% as opposed to 11.1%, in a Veterans Affairs study), with a 0.05% type I error, and with statistical power of 80%. In this example, approximately 2,200 persons would be required in each treatment arm (<http://department.obg.cuhk.edu.hk/researchsupport/Sample_size_Comp2Prop.asp>). These double-digit event rates assume a population at increased risk for clinical cardiac events then traditionally enrolled in studies of type 2 diabetes for regulatory filing.
Applications to the Avandia versus Actos Head-to-Head Clinical Trial
Consistent with the conclusions of Hochman & McCormick (2010), GSK initiated the head-to-head trial of the two launched glitazones, Avandia versus Takeda/Lilly’s Actos (pioglitazone), only when mandated by the FDA (morethanmedicine.us.gsk.com, 8/23/10). This occurred following the release of the Nissen & Wolski (2007) results pointing to increased cardiac-related deaths with Avandia, and the precipitous loss of revenue.

GSK has been accused of being less than transparent in the process of evaluating Avandia, including by Dr. Nissen, who accused GSK of attempting to “censor public debate” and that the company was a “grave threat to academic freedom” (pharmagossip.com, 5/01/10). The FDA’s Thomas Marciniak, team leader of cardiovascular products, who questioned event processing within GSK’s initial randomized study, RECORD, addressed Avandia and cardiovascular concerns (dailyfinance.com, 7/13/10).

One can even point to the title of the trial of Avastin versus Actos: “Thiazolidinedione Intervention with Vitamin D Evaluation” (TIDE; clinicaltrials.gov #: NCT00879970), which does not lead one to assume that this is a rare, double-blinded, head-to-head trial of Avandia versus Actos in terms of clinical cardiac outcomes. One might have speculated that the focus was on an interactive effect of each glitazone in combination with vitamin D.

This confusion adds support to the claim that GSK may have been attempting to hide the true research question addressed by the TIDE trial. The lack of transparency may have well contributed to the slow recruitment into the TIDE trial, as only 1,100 of the anticipated 16,000 patients had been recruited by mid-July 2010 (associatedpress.com, 7/21/10).

But why did GSK anticipate 16,000 patients to be enrolled, when this subject number far exceeds any reasonable statistical power analysis needed to answer the important research question of the two glitazones, sans vitamin D?

In the TIDE trial, post-MI patients were eligible after thirty days from their acute event, although patients with heart failure (New York Heart Failure Class II to IV) were excluded. Given that type 2 diabetes has been recognized as a risk factor for a clinical cardiac event equivalent to a MI (Grundy, et al., 2004), the TIDE trial would require perhaps only a moderately increased sample size as compared to the 4,500 in the ACS trials. Increasing enrollment by about 1/3, would yield a sample size of approximately 6,000 patients in a two-arm trial.

Returning to the topic of the 16,000-patient TIDE trial, GSK may have had two motivations to conduct such an over-enrolled study. First, the huge sample may have been employed to extend the duration of the trial, and, in turn, the time to an empiric answer to the research question, in the hope that Avandia would remain on the market, under normal commercial conditions (i.e., not marginalized, as what occurred). The longer that no answer emerged, under the normal circumstance, GSK could presumably preserve close to the $3.3 billion in revenue generated in 2006. Second, such a large sample size, allows GSK to respond, if the overall impact clinically of Actos in terms of cardiac events, is superior to that of Avandia. That is, the huge sample would allow for post-hoc analysis to discover potential sub-groups in which Avandia may have performed better than Actos.
These are moot points, though, as the FDA “placed a partial hold” on the Avandia versus Actos TIDE clinical trial (fda.gov, 7/21/10) Ironically, the same panel voted 20 to 10 to keep the Avandia versus Actos trial alive, if the FDA votes to retain Avandia on the market. Thus, US regulators have essentially overturned this aspect of the panel vote. In an update to the clinical trial, GSK has noted tersely that the “trial has been terminated” (clinicaltrials.gov, 4/07/11).

The “hold to termination” of the Avandia TIDE trial was not a surprise, given that US Senators, Max Baucus (D-Mont.) and Chuck Grassley (R-Iowa), had released a report in the second quarter of 2010 (2Q10) questioning the comparative trial on ethical grounds. The focus was an FDA analysis that estimated the drug caused approximately 47,000 excess heart attacks between 1999 and 2007, among Medicare patients 65 years and older (Graham, et al., 2010). When younger type 2 diabetic patients are included, estimates approach 100,000 excess deaths attributed to Avandia, relative to Actos.

Grassley has been a critic of the agency for several years, with a particular focus on the approval of the antibiotic to treat acute bronchitic and other respiratory infections, Sanofi’s Ketek (abcnews.com, 6/14/06). Grassley reportedly focused on the FDA’s willingness to overlook fraudulent safety data and questionable trial data to keep an application on track for approval (invivoblog.com, 3/04/08). One physician was sentenced to five years in prison for falsifying Ketek safety test results (abcnews.com, 6/14/06). Senator Grassley, though, was stymied in attempts to interview FDA members about this scandal. After reports of four deaths and 35 liver failures with Ketek, in 1Q07, the FDA banned Sanofi from selling Ketek to treat acute bronchitis or sinusitis, while commercial sale for pneumonia was sustained with new warnings (Bloomberg.com, 2/12/07). Thus, the FDA decision to halt the TIDE trial may have been motivated by a desire not to engage in another battle with the senior Senator from Iowa, when GSK did not seem motivated appropriately to deliver the product in a timely manner.

Still, the decision by the FDA to place a “partial clinical hold” on the TIDE trial of the two launched glitazones, Avandia versus Actos (associatedpress.com, 7/21/10), leading to the termination of one of the few, genuine head-to-head clinical trials of any drugs, is cause for concern. Indeed, the FDA might have considered an alternative strategy with regard to the trial. That is, give GSK a deadline to recruit sufficient patients to answer the research question, 6,000 rather than 16,000 offered, enrolled fully within 18 months or Avandia would be removed from the market. I suspect that given this contingency, GSK would deliver a fully recruited study within the time constraint.

This approach has been echoed by Dr. Richard Pazdur, head of the FDA’s Office of Oncology Drugs, who reportedly indicated that the regulatory agency will require confirmatory studies, with completion dates, in the circumstance of companies attempting to convert accelerated approval to full approval for cancer drugs (pharmalot.com/Silverman, 7/20/10). This approach underscores the FDA’s attempt to rescind labeling of Roche’s Avastin (bevacizumab) in the treatment of advanced breast cancer (pharmalot.com, 4/08/11).

The bottom line is that given the paucity of studies designed to evaluate efficacy : safety in true head-to-head clinical trials (Hochman & McCormick, 2010), the agency, arguably, should have done more to fend off political pressure, and GSK’s inertia to preserve the “existence of a threatened specie”.
References


Implications for Roche:

Roche expects a global regulatory submission by mid-2012, about a two-year delay from the initial submission.

Recognizing the shifting tides of greater reliance on OS versus PFS, and the need for adequate control groups for regulatory approval.

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